UsAgainstAlzheimer's

Alzheimer's Talks
with Dr. Rudy Tanzi
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Note: Transcripts are edited for content and clarity.

George Vradenburg: Welcome to Alzheimer's Talks. This is a monthly teleconference series presented by UsAgainstAlzheimer's, where we seek to connect you with leaders in this field who are working to stop the disease. My name is George Vradenburg, the Chairman and Co-founder of UsAgainstAlzheimer's which is a disruptive nonprofit, a patient-centered organization seeking to transform the fight against Alzheimer's.

Join us at www.UsAgainstAlzheimers.org. We will give you something every week that you can do in just a few seconds that will actually increase the numbers of people that are asking someone either a congressman, a senator, the president, a research organization or an industry member to speed up their work in this disease. Please join us.

I just wanted to report briefly on the Summit that we held here in Washington D.C. at the end of September. We had several hundred people from around the country coming here to talk to their members of Congress. We had over 120 visits, roughly a quarter of the Congress was touched on the day that we all went up to the hill, but it was preceded by 2 days of summit activities.

One was devoted entirely to communities of color, the disparate impact of the disease in terms of incidence and prevalence, and the disparate participation by communities of color in clinical trials and in the research agenda. Out of that came a real directed effort at a greater inclusion on the way to the cure.

The second full day was a robust day full of panels: persons with dementia and their caregivers, industry and research leaders who talked about where we are on the national goal to find a means of prevention and treatment of the disease by 2025, and a panel on the economics of the disease. We also had an announcement of the Alzheimer's Party. Since my wife is a Democrat and I'm a Republican we tend to cancel each other's vote. We decided to join the same party and we're calling it the Alzheimer's Party. We're asking members of Congress to sign up. We have about 25 Congressmen and women and about 20 Senators signed up so far, and we will obviously continue to pursue this as we gain a new Congress in January.

At the end of a very powerful day, we had a dinner of 600 people. Laura Bush was interviewed by Diane Rehm. Laura Bush's father died of the disease and her mother now has dementia. She's committed to join our efforts in fight against Alzheimer's. After a little talking and pulling, Diane Rehm persuaded her to ask her husband to participate as well. All the other first ladies participated by video. We honored Nancy Pelosi, the Minority Leader of the house as well as Kelly Ayotte, a prominent Republican senator from New Hampshire. We honored Dave Ricks, the incoming CEO of Eli Lilly after their significant investments in the leadership to find a cure. It was a powerful evening and we were greatly gratified about what we called "The First National Convention of The Alzheimer's Movement".

Today our guest is Dr. Rudy Tanzi. He is the Vice Chair of Neurology and Director of the Genetics and Aging Research Unit at Massachusetts General Hospital and a Joseph P. and Rose F. Kennedy Professor of Neurology

at Harvard Medical School. Joe Kennedy was at our summit by the way. Dr. Tanzi was chosen by the Geoffrey Beene Foundation as a "Rock Star of Science". He's also a Founding Member of our researchers' network.

Just a personal note. Rudy is one hell of a musician, a harmonica player. He played with Joe Perry of Aerosmith at a couple of our events. He's a talented guy. He actually appears now on a CD with Joe Perry. He is really a rock star of science.

Dr. Tanzi co-discovered all 3 familial early-onset Alzheimer's disease genes. He's published roughly 500 scientific papers including the top 3 most cited papers in the field of Alzheimer's disease research, and remarkably he looks like he's 35.

Today we're fortunate to have Dr. Tanzi joining us to share with us his fascinating new work on a microbial hypothesis of the causes of Alzheimer's disease. Postulating that microbial pathogens can rapidly induce amyloid plaques deposition as a defense mechanism of the brain's innate immune system. He will also discuss what it means for the etiology of Alzheimer's disease and implications for drug development.

Just as a reminder for you all, if you have a question at any time press star 3 on your phone. By pressing star 3, you'll be placed into a queue, have your question ready for a member of our staff and we'll get you online as soon as we can. If you're listening to us online, you can type your question in the box and we'll get to as many as possible after the opening presentation. Please note that Dr. Tanzi, like all of our guests, is not able to answer personal medical questions.

Rudy, thank you so much for joining us today. We look forward to your opening comments and the subsequent questions.

Dr. Rudy Tanzi: Thanks George. Thanks everyone for joining today in this discussion of a very exciting new topic in Alzheimer's disease.

George, actually I played harmonica for Congress with Joe Perry, but I play keyboards normally. Thanks to the Rock Stars of Science program that you and Meryl Comer started. I now play quite often with Joe Perry and Aerosmith. In fact, after this call, I'm heading to the studio to start another new album with those guys. You relaunched my music career on the side, but believe me, it's not taking me away from science. It actually helps feed the creativity. Thank you for that.

I know everyone on this call knows Alzheimer's to some extent, but I think to begin this presentation, let's just review the 3 major pathologies of Alzheimer's disease. They are the senile plaques made of the beta-amyloid material, which is strewn like boulders outside of nerve cells. You have the tangles which form inside of neurons which, as Alzheimer himself put it decades ago, choke the neurons from inside and kill them. As this chaos is happening, neurons are dying, tangles are forming, plaques are depositing, the brain reacts to that with inflammation.

Inflammation is a reaction of the brain's innate immune system to protect itself. Frankly, when the brain sees so many nerve cells dying and the amyloid depositing, it assumes there is some type of foreign challenge. It's trying to protect itself with what are called glial cells that are getting activated into this inflammatory state. Although it's well intended, many of us believe that it's inflammation that really pushes you down the slippery slope. That the plaques and tangles kind of push you up the mountain, but you can live there for a while, but it's when the brain reacts to inflammation that you get pushed down the slope.

Now for a long time, there have been groups of people around the world who have said, "Hey, we believe that it's infection in the brain that causes inflammation and maybe those plaques and tangles are just markers. They're just ghosts. They're just side consequences. The real story is that there is an infection in the brain which is causing that inflammation and that's why the brain goes downhill."

That was a lot to take for me because having been one of the people who discovered the early-onset genes that cause amyloid deposition and seeing results from our, what's called, Alzheimer's-in-a-Dish model we developed a couple years ago with Doo Yeon Kim; we can recapitulate a mini-Alzheimer's brain in a dish. I think the evidence is clearer than ever that amyloid is sufficient to trigger the tangles. Amyloid also triggers inflammation and as tangles kill nerve cells, you get more inflammation. So I believe amyloid triggers this disease.

There are other ways to get tangles. You can get lots of bangs to the head, concussions, traumatic brain injury, you go directly to tangles and inflammation without the need for amyloid. But the most common way to get tangles and inflammation as we grow older is amyloid building up in the brain.

Now where does that leave us with all the folks who've been saying infection, infection for so long? Some of these people are like Ruth Itzhaki who said it was herpes virus and Brian Balin who said it was chlamydia bacteria. We have a whole host of folks who say it's Lyme disease pathogens like Borrelia. Others who say it's candida or yeast. The fact is I think everyone is right. The infection people are right about the roles of these microbial pathogens and the amyloid people are right about the role of amyloid. What I'd like to do is tell you how these two hypotheses are actually merged together and make a lot more sense when you consider them together.

The idea that amyloid causes Alzheimer's really began back in 1983 or '84. George Glenner was a scientist in San Diego and he discovered the plaque is made of this little protein called amyloid beta-protein as he named it. Then we and others, a few years later, found a gene that makes it and posited that that would be the first Alzheimer's gene. Of course mutations would be found later that validated the fact that that's the first Alzheimer's gene.

The problem that led to the debate about amyloid was there for a good couple of decades when you put those Alzheimer's genes into mice and you have them make amyloid in the mouse, yeah, the mouse would eventually get enough inflammation to become cognitively impaired, but you didn't get the tangles. Because the amyloids did not drive to tangles in mice, that led to the question about whether amyloid really triggers the disease.

It's just over the last couple of years that we came to a striking realization that humans are not 150 pound mice. Mice are very different than humans. You just look at them and you can tell that. It wasn't until we could build human stem cell derived brain organ origin in a dish, we recapitulate the disease like we did in a dish. We can see clearly now with human neurons growing in a 3D gel matrix mimicking the brain, amyloid is sufficient to drive to tangle pathology, which I think really helped put that debate to rest.

When I present this story publicly, there is always a really good question. "Okay. Fine. We'll believe you. The amyloid is accumulating in the brain as we get older. It's accumulating 20 years before any symptoms, it's driving the tangles and the inflammation, and that's eventually leading to dementia. The question, why do we have amyloid? Where is the amyloid coming from?" For about 1% of cases, I can answer that question. I can say, "Well, they have these mutations in these early-onset familial Alzheimer's genes like amyloid precursor protein, APP, presenilin-1, presenilin-2 that we and others co-discovered but in 99% we don't know why they

make amyloid."

The answer has always been, amyloid is just junk. It's just now we're living long enough to have this junk accumulate in the brain kind of like an old city where garbage collection isn't perfect and eventually that garbage starts to accumulate into streets and you see it. It's just junk that accumulates with age. I bought into that for a long time. Then one day my colleague, Rob Moir, an Australian scientist, extremely bright, he trained with Barry Marshall in Australia. As you remember Barry Marshall claimed that ulcers are caused by bacteria called Helicobacter pylori and no one believed him. So he drank the bacteria and gave himself an ulcer and he got a Nobel prize. I'm not going to do that.

Rob also thinks out of the box, and especially on Fridays when we have our beer hour and after a couple of Coronas, Rob is really thinking out of the box. He said, "Look at this," he said, "Amyloid beta protein has been around on this planet for over 400 million years. If you look back to the coelacanth, which is like a living fossil fish, it has an amyloid precursor protein gene, APP, and its amyloid beta protein sequence is identical to that of humans. How can this thing that's been around for 400 million years being produced in different species be without any function whatsoever?"

With further investigation, he noticed an uncanny similarity to a type of protein in the body called antimicrobial peptides. As you might guess, these are small proteins or peptides that fight against pathogens, against microbial pathogens. There are a whole bunch of them known. They're part of what's called the body's innate immune system and the brain only has an innate immune system. The body uses T-cells and B-cells and antibodies, the brain does not. The brain has glial cells which fight its battles by shooting out oxygen-based bullets like free radicals causing a lot of friendly fire and collateral damage on nerve cells. That's why the inflammation kills so many nerve cells.

But also, you produce these antimicrobial peptides known as things like, defensins, protegrins, temporins, LL-37. There is a whole literature on them. These little peptides are 12 to 50 amino acids long. Well amyloid beta protein, I'll call it A-beta for short, is about 37 to 43 amino acids long. They are charged like A-beta. They take on both what's called alpha helical and beta sheet combination. You can go through about three pages of Excel files showing the common features between amyloid beta protein and known antimicrobial peptides.

Further, if you treat Alzheimer's as amyloidosis of the brain, just like George Glenner originally said, there are three other amyloidosis in the body. There is amyloidosis of the eye, amyloidosis of the seminal vesicles, and amyloidosis of the aortic medial artery. In all three cases, those amyloids are made from proteins that are antimicrobial peptides. It turns out that antimicrobial peptides, the way they work, the way they fight microbes is that eventually they form amyloids. The question was, could amyloid beta protein or A-beta be one of these and could it be that the amyloids are accumulating in the brain as a defense response against microbes?

Of course here somebody might say, "Wait a minute. Wait a minute The brain is sterile. The brain has a blood-brain barrier. There are no pathogens in the brain." Well guess again; there are plenty of viruses in the brain and as we get older, our blood-brain barrier begins to become a little less strong and starts to breakdown. Our adaptive immunity starts to become a little less strong and now microbial pathogens can build up. And it’s clear upon autopsy analysis of brains that we do have plenty of microbes in our brain. That our brains are not sterile.

What we did was back in 2010, we had a graduate student, a brave graduate student, Stephanie Soscia, who tackled this hypothesis and did very simple experiments. She took 20 or so different clinical pathogens like staphylococcus and listeria, E. coli, yeast like candida albicans, and she said if I test amyloid beta protein head-

to-head against a known antimicrobial peptide that kills a lot of these pathogens, let's see how it does. It turned out it did extraordinarily well. It was very effective against candida, against E. Coli, against different types of staphylococcus, listeria.

It was a small paper because everything was done in Petri dishes and test tubes. The only thing we did with human materials, we showed that the brains with amyloid in them from Alzheimer's patients had more antimicrobial activity than brains without amyloid. We showed that if we took the amyloid out of that brain with an antibody that you lost that antimicrobial activity, but otherwise it was very much an in vitro study. We published it in a fairly humble journal PLOS One, but Gina Kolata picked up the story and it turned into a front-page science time story in the New York Times. We said, "Uh-oh, now we've done it."

Now you've got to worry about what's called the Schopenhauer rules of scientific discovery. Schopenhauer said for every new idea that first it's ridiculed, and secondly, it's violently opposed until third it becomes taken as self-evident. Lots of my close buddies and colleagues and scientists were calling. They were saying, "Tanzi, what the heck are you talking about? You're saying that bugs cause Alzheimer's disease?" I'm saying, "No, no, no. I'm not saying that yet. I'm just saying that amyloid beta protein looks a lot like an antimicrobial peptide but now the real work begins." This was back in 2010.

The real work meant that we had to look in different animal models and show that beta amyloid was antimicrobial, that it did help fight infection, that it would help different animal models survive with the amyloid there versus not. The results that I'm going to tell you about took 6 years to produce. The paper we published recently in Science Translational Medicine, there are literally 60 pages of supplemental data because we wanted to make sure when this paper came out, that we were at least jumping right from the ridicule stage maybe into the violently opposed but not so much stage. As it turned out, we did very well with the public and scientific response to our paper because, I think, we took so much time and care to put out so much data and do so many controls.

What did we find? First, we found that if you just take the human neurons and grow them in a dish the way we do including the 3D cultures that sure enough if amyloid is there, that you get more protection against the infection. For example, using salmonella or using yeast candida to attack the cells, both of these will kill nerve cells.

Then we went to nematodes, little dirt worms, C. elegans. We had C. elegans that were either just regular, wild type, or we had ones that were transgenically producing human amyloid in their gut wall. Again we attacked those C. elegans with yeast. It's really quite a sight to see yeast attacking a nematode. They actually go inside the nematode and then they shoot spikes out through the worm. It looks like a scene from the movie Aliens. It's quite dramatic. And we were able to protect against that by having amyloid in the gut wall.

Then we went on to Drosophila and showed there with a different model that we could protect Drosophila against yeast infection. But most convincingly, we went to mice and we took Alzheimer's mice versus control mice. We showed that if you give an Alzheimer's mouse meningitis with salmonella in the brain versus a control mouse, that the mouse with the amyloid in the brain survived a lot longer and a lot better than just mice without the amyloid, the control mice. If you take mice that don't make amyloid, give them knockouts of the APP gene, they survived less well. All these data suggested in these infection models that amyloid can help protect you against infection.

Then the question became how? There, all we had to do, and I say we it was really Rob Moir and his lab in collaboration with my lab, our labs are in the same unit here that I direct at Mass General, we were able to ask,

what's going on? We were able to see from the literature how other known antimicrobial peptides do their job. And here is what they're known to do: When the microbe comes in, it could be herpes virus, it could be yeast, it could be a bacterium, all of these microbial pathogens have sugars, carbohydrates, on their cell walls. The known antimicrobial peptides, like LL-37, bind to those sugars on the cell wall and then prevent the microbe from attacking the human cell. They find a sugar or carbohydrate, the antimicrobial peptide binds to it, and now it prevents the adhesion of the clinical pathogen to the cell wall.

Sure enough, in all the models we looked at that's what the amyloid was doing. It was binding to the sugars. We found the sugar-binding site. We were even able to compete away that binding, prevent the amyloid beta protein from binding to the sugar site and we lost that anti-infection protection, so that was a check.

Then the next thing antimicrobial peptides do is after they block the adhesion, the antimicrobial peptides start to form little clumps called oligomers and they start to form little baby fibrils. It sounds familiar, right? That's what the amyloid beta protein does, it forms oligomers and fibrils on their way to a plaque. Eventually, what do known antimicrobial peptides do? They form fibrils. They form webs. These are called nanonets in the innate immune literature. They form actual webs of fibrils that trap the bacterium, yeast or virus. Now it's entombed in a web of gunk that basically is like amyloid. It's almost like if you picture Spider-Man shooting that web at the villain and capturing him. That's what they're doing. That's how antimicrobial peptides work and sure enough that's exactly what we saw amyloid beta protein do in all of these different models, against yeast, against bacteria. Then more recently, we've seen that this is what happens against herpes simplex virus 1.

All of these folks who over the last decades have been clamoring herpes simplex virus 1 and chlamydia, Borrelia that's what causes Alzheimer's, they could be right. But the reason is not because those infections are directly causing cell death, what we're seeing is that they are actually triggering the deposition and the need for amyloid to entomb them to protect the brain against these pathogens.

I want to leave time for questions because I realize any new hypothesis like this will lead to a lot of questions. What I've told you so far is that whether it's herpes virus or other viruses, bacteria like salmonella or E. coli or yeast like candida, same mechanism. The amyloid beta protein mediated antimicrobial activity is such that the amyloid protein first binds to cell wall sugars, prevents the adhesion to the host cell, then it packages all these little nasty bugs together - it's called the agglutination - it does that with fibrils, and then eventually it forms a full net to trap that bacterium or virus and that is what we see as plaque in the brain. You see this in other organs, other antimicrobial peptides can create amyloid in a similar way, as I told you earlier.

Now the data that really got me if this wasn't all strange enough, the data that really blew my mind and got me thinking differently about Alzheimer's came from the following experiment. When we were able to put salmonella into the mouse's brain and you're asking does amyloid protect against infection? The answer was yes, but then in the next experiment, we took mice, these were Alzheimer's mice, they were only four weeks old, they are making the amyloid beta protein but they don't yet have plaques. They have no visible plaques yet. There is no pathology you can see yet at four weeks old.

You inject the salmonella into the hippocampus, short-term memory area where you normally see plaques, you wait 48 hours, that's just 2 days, and when you look in that brain section you see that the area of the brain is full of plaque, chock-full of plaque overnight. Now this goes against everything we've ever said. We always thought of a plaque forming slowly over the decades. Even in the mice, plaque is forming slowly over months. You don't normally see that plaque until 5, 6, 7, 8 months old in Alzheimer's mice.

Four-week old mice, overnight, instant plaques. And because the bacterium are actually stained red with a fluorescent dye, you can see that in the center of every plaque, there was one or more bacteria. In fact, in some cases, one bacterium was at the center of one plaque all within 48 hours. This is all proof of concept stuff, but this suggests that perhaps even a tiny bit of microbe that's sneaks into the brain is able to rapidly seed. This is the key word that we don't think enough about. We always talk about amyloid beta protein production versus clearance. We think about like plumbing, you get the spigot on too high is the drain clearing the water? We think about production and clearance of amyloid, this is seeding, seeding called nucleation. This is how antimicrobial peptides work is that the actual microbial pathogen that the antimicrobial peptide is protecting you against is actually seeding the amyloid. As the microbe comes in, it actually causes that amyloid web to be formed instantly as a way for that antimicrobial peptide to trap it and protect you. That's exactly what we're seeing.

This suggests that perhaps in Alzheimer's, the reason why we have amyloid is that over decades, small amounts of infection, low-grade infections, asymptomatic, nonclinical infections, be it virus, yeast, bacteria, to be determined, are nucleating and seeding amyloid rapidly. That's the next step is to ask is this going on in humans? Here, we have all of these data, we have proof of concept, amyloid beta protein is an antimicrobial peptide. It worked in all of our model systems. It works against yeast, bacteria, viruses. It rapidly seeds plaques in just 48 hours. In fact, when we use herpes simplex virus 1, we can get plaques to form in those mice in 6 hours. It's even more dramatic than using bacterial like salmonella.

The question then becomes, now well is this really happening in patients? This is our proof of concept work in model systems, mice et cetera, is it really happening to patients? Cure Alzheimer's Fund funded this entire antimicrobial peptide work and then it was leveraged with funding from the NIH after that. Cure Alzheimer's Fund likes to take these high risk potentially big game projects on. They have agreed now along with another foundation called Open Philanthropy, to fund what we're calling the Brain Microbiome Project.

We all know that we have a microbiome, right? We know that we're big spaceships of bacteria. We have about 2 or 3 pounds of bacteria in our gut and they help us to survive. We need those bacteria. They even help control inflammation in the brain from the gut through the gut-brain axis. They help control the blood-brain barrier integrity. What if the brain has its own microbiome? Could it be that as we age, that various microbes are sneaking into the brain, be it virus, bacteria or yeast and that this is what's triggering amyloid little by little and that this is what we've been missing in the equation?

If we think about everything we've done so far from genetics to Alzheimer's-in-a-Dish, saying that amyloid is enough to trigger tangles and Alzheimer's disease pathology, the antimicrobial hypothesis would be the prequel. The prequel because it's saying maybe this is why you're making amyloid in the brain in the first place in most people. If you carry APOE4 allele after the amyloid is made, you're clearing it out of the brain a little less well than a APOE3 person who clears it a little less well than an APOE2 person. All that's after the fact, maybe the reason why we're making amyloid is it's being triggered by microbes.

As part of this Brain Microbiome Project, what we plan to do, and we've already begun, is to look in Alzheimer's brains versus control brains, affected regions versus unaffected regions and look at what types of microbial RNA may be present because you can do what is called RNA seq. That means you are sequencing the RNA in the brain and most of that it's coming from human, but you can also possibly find foreign RNAs from microbes. This is something we've been doing. Like I said, people have done this in the past. They've found herpesvirus. They've found chlamydia. They've found Bolleria. They have found various candida species but they were directly looking for those.

We're saying, let's not look under the lamplight. Let's do this agnostically, totally unbiased. Let's just see all the different foreign RNA that's in the brain coming from microbes, make a catalog, do 100, 200 brains. Secondly, we're going to isolate plaques from Alzheimer's brain, laser capture, isolate the plaques or fluorescent capture and then we're going to sequence inside the plaque to see what type of RNA is there because according to this hypothesis, there should be a tomb of microbes that were trapped by plaques as a way to protect the brain from those microbes.

That's all going on now. Cure Alzheimer's Fund and Open Philanthropy are behind funding this. We're also applying for NIH funding to continue to do this, but it's a whole new area of Alzheimer's disease research. Ultimately, if we can find some common suspects that look like they're driving the need for amyloid and nucleating and seeding amyloid as a defense mechanism of the brain, then we can start targeting those particular pathogens, either directly with brain permeable antibodies. Luckily, we have a couple of those: one is PBT2 from Prana Biotechnology and another is a conjugated antibody that gets into brain. We can think about passive immunotherapy, antibodies against those pathogens. We can think about vaccinating against those particular pathogens. The way we would vaccinate against measles or the like.

This is all very much futuristic, what I'm talking about right now, but I think we're well on our way toward at least determining whether we can go down that route. That's the antimicrobial story. I hope I've left enough time for some questions.

George Vradenburg: You're getting some questions and we'll get to them in just a second. Just as a reminder to anyone, if you do have a question press star 3. You'll get into a question queue through a member of our staff and we'll get to your question to Dr. Tanzi.

We have Melissa Jones that has written in a question. It sounds like an antibacterial type treatment would be an option to keep the microbes at bay to begin with, but we know we don't want to overuse antibiotics. Is there a space for an antibiotic type of treatment that doesn't fuel future superbugs?

Dr. Rudy Tanzi: Look, most antibiotics don't get into the brain anyway. If you're going to use an antibiotic, it has to be modified to get into the brain and it is a concern. A drug I've been working on for a long time is PBT2 which comes from Prana Biotechnology, a company that I actually started in my lab. PBT2 is aimed at preventing the amyloid from aggregating and forming.

It turns out that PBT2 is also a very potent antibiotic and antiviral and it gets into the brain. That's one way you wouldn't have to worry about classic antibiotic effects in the body in terms of resistance but could be one way to do it.

The other ways to do it, I'm thinking about vaccination, thinking about antibodies, passive immunization with antibodies is the way we target amyloid already with like Aducanumab or Solanezumab, et cetera. There are different ways to think about doing this but I think that's a very valid concern. I would not think that classic antibiotics like penicillin or like amoxicillin would be used here. This would be a very specialized type of drug.

George Vradenburg: Let me ask, this is coming from me, how would you vaccinate against all the full range of pathogens that might be triggering this beta amyloid reaction?

Dr. Rudy Tanzi: That's an excellent question. I don't think you can. For any antimicrobial peptide, most of them have at least a spectrum activity against viruses, bacteria, and yeast. We see that amyloid beta protein works a little bit better against candida than any other known antimicrobial peptide.

I think that we have to take this journey and start the project. We have to look in the brain and ask as we age and particularly in Alzheimer's patient's brain, what are the most common pathogens? Are there ones that seem to be more prevalent than others that we can start to target? But that may not do the job. There may be others that can still trigger the amyloid and maybe you'll never vaccinate against all of them.

But if we can find the main ones, if there are certain ones ... I think I can just say that based on the early data and we're collaborating with Eric Schadt's group at Mount Sinai now, based on the early data, we may get surprised. We may find there are some common microbes that could be targeted and put a big dent in this. I'm optimistic but I'd share your concern in the question.

George Vradenburg: I guess one of the questions is whether there are other antimicrobial actors in the brain? If that's the case, are they specialized by the nature of the pathogen they're attacking?

Dr. Rudy Tanzi: Yes. The brain has many antimicrobial peptides. In fact, when we look in the mice where APP, the amyloid precursor protein, has been knocked out and amyloid beta protein is not made, you get a reduction in the ability to protect against infection. But you don't completely remove defense because there are many redundant antimicrobial peptides in the brain and in the body that cover for each other, so amyloid beta protein would be one of them.

Now why that particular one accumulates so much in the brain ... Is it that it's being used more or is it that once you use it and you trigger the amyloid deposition, as an antimicrobial substance, is it just tougher to get rid of? In other words, like what we see in those other amyloids I mentioned in the heart and in the eye, there are certain antimicrobial peptides that form amyloids so they're just tougher. It's more difficult to get rid of them, so they tend to stick around then cause problems.

That's what I think is going on here is that the amyloid beta protein is one antimicrobial peptide in the brain, but the amyloid that it makes is much more difficult to get rid of and it hangs around for a long time. And according to Alzheimer's-in-a-Dish model and genetics, that's then triggering the tangles and the rest of the disease.

George Vradenburg: We've got a question here from Robert Carrico. Robert, would you like to ask your question?

Question: Yes. Okay. I was just wondering how this theory helps to explain early-onset Alzheimer's, and in general if there is this protective benefit, why is it not operative with younger brains?

Dr. Rudy Tanzi: Okay. If it's early-onset Alzheimer's disease with onset under 60 or 50, usually it's familial Alzheimer's disease gene mutations that are getting you to the amyloid deposition, presumably without the need for microbes and clinical pathogens.

The second part of your question, we believe that as we get older, our brains start to accumulate these microbes. In other words, when you're younger and your blood-brain barrier is quite strong, you're probably keeping a lot of these microbes out of the brain. As you get older, and if you look at the work of Zlokovic and other recent studies that show that the blood-brain barrier starts to break down in integrity as we get older, especially around the hippocampus that's affected in Alzheimer's. Our adaptive immunity, our immunity against microbial pathogens starts to go downhill as we get older. We get sick more often.

I think the combination of just getting older and having more ability for microbes to enter the brain is when you start triggering more amyloid. It may be why you don't really start seeing a lot of amyloid deposition in the brain in most people under 40 years old. That's what the hypothesis will predict. We can test all this now, but that's what we predict.

George Vradenburg: What are the potential interventions that might strengthen the microvascular structures so that you in fact you have a blood-brain barrier that's more protective of the brain?

Dr. Rudy Tanzi: The typical ones: exercise reduces neurogenesis, it can also reduce inflammation; and sleep, 7 to 8 hours of sleep, which everyone should try for religiously now. It's when the brain clears itself out of amyloid, so you get the natural clearance of the amyloid from the brain by your glymphatic system as you sleep.

I think diet is probably number one here because there is increasing data that says your gut microbiome, your bacteria in your gut that interact through various signals with your brain, this is the gut-brain axis which involves the Vagus nerve, that what will happen is that the gut microbiome has been shown to dramatically affect the integrity of the blood-brain barrier. In fact, Sangram Sisodia and I just published a paper showing that when you alter the gut microbiome, you traumatically affect Alzheimer's pathology in mice.

I think that what I'm doing personally, given that I'm now getting to an age where I'm thinking about this stuff. I just turned 58. I'm taking probiotics. In the morning I drink a cup of kefir, which is a liquid yogurt with live cultures in it. I take a probiotic with living bacteria. I'm feeding my gut microbiome because the data is so strong now that your gut microbiome when healthy is helping to stave off inflammation in the brain and also helping to preserve your blood-brain barrier.

In fact, I just hired a new postdoc who is an expert in the gut microbiome to study exactly this, what is the effect of the microbiome on the blood-brain barrier and could this be affecting whether pathogens are getting into the brain?

George Vradenburg: We had a very technical and interesting question from Wei Cao, I hope I pronounced that correctly. Antimicrobial peptides are normally produced by phagocytes in the periphery during microbial infection. Why do neurons instead of resident immune cells (microglia) elicit primary antimicrobial response in the brain? I can't believe I even read that.

Dr. Rudy Tanzi: It was very good, George. You did a great job.

George Vradenburg: That wasn't my question!

Dr. Rudy Tanzi: Yeah. Look, amyloid beta protein is not just made by neurons. It's made by neurons. It's made by astrocytes. It's even made by microglial cells. I don't think you have to posit that only neurons are doing this, but everything is different in the brain. The brain has its own unique innate immune system so I think it's hard to apply the same rules to the periphery in the brain, but the simple answer is that amyloid APP is not just a neuron. An amyloid beta protein is actually made by a number of different cells in the brain.

It does beg the question of, what cell is the main source of amyloid beta protein as an antimicrobial peptide? That I don't think we know for sure. I think there you'd have to really ask that question in a lab setting and look at it. So to the question, I think just off the cuff I would say, look, it's not just neurons making amyloid. It's glial cells as well and we have to find out for the antimicrobial peptide which cell is mainly pumping that out. It

could be all of them.

George Vradenburg: We had a question come in before the call from Edward McGhee in Concord, California. Why does the disease go fast in some but slow in others? Your thesis would suggest that the rate of pathogen build up in the brain can vary based on a number of factors but including the quality of your microvascular, right? In fact, that could be a thesis about why we do progress at different rates?

Dr. Rudy Tanzi: Yeah. I think we're talking about progression and if I understand it, so you mean after the disease is first diagnosed?

George Vradenburg: Why do some people build it slowly and some people build it quickly?

Dr. Rudy Tanzi: I think you have to look at everything from genetics to lifestyle when asking about effects on amyloid deposition. Amyloid deposition as a function of seeding where we would bring in the antimicrobial response in the microbial seeding of amyloid. Also amyloid deposition as a function of clearance, where you have to bring in APOE, where E3 does better than E4. E4 is a risk factor. E2 does better than E3. E2 is protective.

We also have to look at the rate at which tangles are created in response to amyloid or other insults to the brain and how our tangles spread. I think most importantly; I would say inflammation. I think how the brain reacts to plaque, tangles, and neurodegeneration with inflammation differs between people based on genetics and again also on lifestyle because again your gut microbiome is also affecting inflammation in your brain. Your genes are affecting inflammation.

The biggest set of new genes that we found in Alzheimer's disease as part of our Alzheimer's genome project that Cure Alzheimer's Fund supports are innate immune genes. Genes involved in inflammation and innate immunity. Genes like TREM2 and the one we found years ago CD33, other genes as well. So, I think you have to look at innate immune genes.

Interestingly, we have a small set of brains that we got from Teresa Gomez-Isla here at Mass General, what they call resilient brains. These are from people who die in their 80s with no cognitive problems but the brains were then found to be full of amyloid plaques and in many cases tangles, enough to say hey, this is Alzheimer's, but no they had no cognitive problems or dementia.

What those brains all had in common was no gliosis, no inflammation. Somehow, despite all of those plaques and tangles, they didn't have inflammation and they never got demented, which is good news because it says maybe we can live for quite a long time with lots of plaques and tangles if there is no inflammation. We did a whole genome sequencing on those brains and we have now found some mutations in some of those innate, immune-related Alzheimer’s genes that may be protective and we're testing those now in different models.

George Vradenburg: I've got a question here from Laura. Some are interpreting your work to argue that amyloid is actually protective and therefore it should not be removed. Can you comment?

Dr. Rudy Tanzi: Well, I think amyloid is protective but I think too much of it is bad. I think it's all about balance. It's just like cholesterol. You look at how much cholesterol you have and you dial it down to a safe level, you don't wipe it out. It's very analogous here. We look at amyloid accumulation in the brain by imaging which we can do now. If you're 50 years old and the amyloid in your brain puts you into the 70th percentile for amyloid load, we need to bring down. You have too much, so you think about ways to do that.

Some of these drugs like we're working on gamma-secretase modulators that we have going into trials. There is PBT2. There is beta-secretase inhibitors. There is the antibodies the Aducanumab and Solanezumab, all these aimed at amyloid. You have to hit the amyloid very early before symptoms, but I think you have to gauge how much amyloid you remove so as to not completely wipe it out. This is a message we're trying to send out along with these findings. I think it's a great question, it's all a matter of balance.

George Vradenburg: A question here from James Boland from Idaho Falls. James, would you like to ask your question, please?

Question: My question is, what is the relationship between traumatic brain injury and these various other things? Typically, as I understand it, that does not normally lead to memory problems until later on, et cetera. And part of this question is, what if you treat traumatic brain injury with vitamins, especially vitamin B12 and omega-3?

Dr. Rudy Tanzi: Traumatic brain injury gets you directly to inflammation and tangles without the need for amyloid. The most common form of dementia in the elderly is Alzheimer's, where I think that the combined data say amyloid is what's driving the tangle formation, the cell death and inflammation. Of course cell death is driving even more inflammation.

Bangs to the head, as we've seen, I published a paper with Lee Goldstein and Ann McKee a few years ago looking at athletes and bomb blast victims where we saw that these folks who have traumatic brain injury, directly get tangles and inflammation very quickly. Sam Gandy in New York has shown by tau tangle imaging, then CTE you see tangles accumulating in the brain. You get to tangles and inflammation without the need for amyloid with bangs to the head is the bottom line.

What do we do for soldiers? What do we do for athletes who are getting head injuries more common than others? I actually I'm helping to consult on this very topic with the New England Patriots right now. We've had some very fascinating meetings with Bill Belichick and the team about what can we do, working with a nutritionist there, to help offset the effects of head bangs.

How can we use that in general for health? I think you said the right thing, which is omega-3s are just so important. There is increasing data. I just gave a talk at Tufts last week on nutrition in the brain. Gene Bowman was there from Nestlé in Lausanne, Switzerland talking about studies he had done and showing that high doses of omega-3s like DHA and EPA, are dramatically good at helping to arrest inflammation in the brain. I personally take plant-derived DHA and EPA just because I'm a little afraid of fish oil and the heavy metal content in our fish oil today. I feel that plant (algae)-derived or vegan DHA and EPA is safer, so I take that myself.

I think there is another study that came out of China that showed B12 plus DHA and EPA is a more potent combination than DHA and EPA alone. So, I think you're on the right track what you just named. I would have said the same. B12, DHA and EPA as omega-3s preferably plant-based. I would also add to that vitamin D3, especially if you're deficient, as another important factor.

George Vradenburg: I'm going to ask one last question from Ann Napoletan. How likely do you feel it is that we'll have proven disease-modifying drugs in the next 5 years?

Dr. Rudy Tanzi: If we're talking about modifying amyloid pathology itself, which I believe will go a long way to

prevent the symptoms from occurring in those who are pre-symptomatic, I think within 5 years there is a very good likelihood we'll have drugs that can lower amyloid safely and effectively. If, however, the FDA requires that we show those same drugs improve cognition in patients who already have the disease versus using them to prevent the symptoms of the disease in those who have amyloid in their brain, than it is going to be longer than 5 years.

I think right now the bar is raised too high and that the FDA is expecting an anti-amyloid drug to improve cognition in a patient with the disease. That might be saying, here is a cancer patient whose tumor is already 3 inches wide and we're just going to give them a drug to stop cell division and expect their organ function to come back. I think we need to reset expectations in our field especially in discussions with the FDA and that I believe if we can hit amyloid pre-symptomatically early on that we can go a long way to preventing the onset of symptoms of this disease.

So I think 5 years is a good bet for hitting progression of the disease at the pathology level, but those drugs might not see the light of day if they're going to wait to see if those effect patients at the cognitive level because you have to do that before symptoms hit. For patients who have this disease, you really have to hit inflammation. I think the clue is coming from genes like CD33 and TREM2. Many, many pharma companies are jumping on CD33, this gene we found in '08 and TREM2 that was found in '13 as targets for microglial inflammation. That's what patients need right now when you already have the disease.

George Vradenburg: Thank you Rudy Tanzi for a very clear and very direct and very compelling kind of case about this new hypothesis. It's fascinating and it leads one down a number of potential routes and responses and the like. Thank you so very much for spending time with us today. I'm sorry, I couldn't get everybody's questions but there are certainly some good ones here.

Our next call will be on Wednesday, November 16 from 3 to 4 pm Eastern with Dr. Laura Baker
who is launching a new study called "EXERT", appropriately named, which is the new NIA-supported multi-site study of exercise to slow disease in mild cognitive impairment. You've heard a good explanation from Rudy about why exercise might well be a hypothesis on how it is that you'd improve your blood-brain barrier.

If you've not already joined UsAgainstAlzheimer's, please go to www.usagainstalzheimers.org/ and sign up. We'll send a recap of this call, invitations to future calls, and important updates and simple ways that you can get involved. I hope you'll join us and add to the hundreds of thousands of people around the country that are with us and taking action every week to impact the pace of the discovery in this disease.

Thanks to everyone on the line for participating. In a couple of weeks, we'll have a copy of the recording and a transcript. As always, please stay on the line if you'd like to leave us a message with a question or comment. We're particularly interested in what you'd like to discuss on future calls. Thank you Rudy Tanzi for doing what you do. Thank you for joining us today and to all of those on the phone, have a good afternoon.